EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PROGESTERONE

Reproductive and Cancer Hazard Assessment Section (RCHAS)
Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency (Cal/EPA)

Progesterone Pharmacokinetics

- Low oral bioavailability
  - Vaginal, nasal, dermal bioavailability
  - Micronized progesterone orally bioavailable
- Short half life (5 min in serum)
- Metabolized in liver
- Activates progesterone receptors

Progesterone Exposure

- Contraception (IUD)
- IVF pregnancy support
- Gynecological disorders
- Hormone replacement therapy
- Supplement/cosmetic
- Livestock growth promoter
- Environmental contaminant

Male Reproductive Effects

- Humans
  - 1958, 8-9 prison volunteers, 50 mg/d i.m., 10 weeks
    - Azoospermia
    - Reduced libido and testicular size
    - Fewer mature sperm in seminiferous tubules
  - 2003, 10 young men, 50 mg/d i.m., 7 days
    - Reduced LH, FSH, testosterone, GNRH response
- Animals
  - Spermatogenesis, monkeys, rabbits, rats
  - Altered sexual development, rats

Female Reproductive Effects

- Humans
  - 1956, 32 women, 300 mg oral
    - Suppressed ovulation
  - 1982, 80 women, progesterone IUD
    - Lower postpartum menstruation
    - Greater milk production, altered composition
- Animals
  - Reduced fertility, several species
  - Altered sexual development
  - Parturition and maternal behavior

Developmental Toxicity-Human

- Malformation
  - Six studies including progesterone- treated women
  - No statistically confirmed associations
- Pregnancy outcome
  - Three prospective random studies
  - No statistically confirmed effects
- Female virilization
  - Confirmed for several progestagens
  - Only case reports for progesterone
- Male hypospadias
  - Progestagen case-control studies
  - Two progesterone studies; no control groups

Developmental Toxicity-Animals

- Pregnancy outcome
  - Rats, intrauterine death and growth retardation
  - Rats, rabbits, altered sex ratio of newborns
  - No increase in malformations
- Altered sexual development
  - Two studies in mice
  - Impaired adult mating in males
  - Enhanced postpartum aggression in females

Developmental Toxicity-Animals

- Female virilization/anogenital distance
  - Nor-testosterone effects confirmed in animals
  - 2/10 progesterone studies found anogenital distance effects
- Male hypospadias/anogenital distance
  - Six studies
  - Increases, decreases, no effects on anogenital distance

Summary of DART Effects Reported for Progesterone

Developmental

- Intrauterine death and reduced fetal weight
- Altered male and female sexual development

Male Reproductive

- Suppressed spermatogenesis
- Reduced fertility, altered sexual development

Female Reproductive

- Suppressed ovulation
- Reduced fertility, altered sexual development